

REMARKS

The Applicants respectfully request reconsideration of this application in view of the above amendments and the following remarks.

35 U.S.C. § 112 Rejection

The Examiner rejects claims 27-30 and 37 under 35 U.S.C. § 112, first paragraph. In particular, the Examiner has asserted that “[t]here is no support in the specification of a composition comprising a compound of formula I and a microorganism such as tuberculosis”.

Firstly, Applicants respectfully submit that of claims 27-30 and 37 only claim 27 recites that the composition comprises tuberculosis. In particular, claims 27-30 and 37 recite as follows:

- 27. The composition of claim 1, further comprising tuberculosis in contact with the diluent.
- 28. The composition of claim 1, further comprising bacteria in contact with the diluent.
- 29. The composition of claim 28, wherein the bacteria comprise mycobacterium.
- 30. The composition of claim 29, wherein the bacteria comprise *Mycobacterium terrae*.
- 37. The composition of claim 19, wherein the amount is effective to kill at least 1×10^6 *Mycobacterium terrae* bacteria in contact with the composition in less than one hour with a bacteria suspension test at a temperature of 20°C.

Secondly, Applicants respectfully submit that all of claims 27-30 and 37 fully comply with 35 U.S.C. § 112, first paragraph. On pages 9-13 of the present patent application, it is disclosed that propanedial compounds have germicidal efficacy, and may be used to form germicidal compositions useful for disinfection or sterilization. In Examples 4 and 5 on pages 11 and 12 of the present patent application it is disclosed that the several germicidal solutions each containing one of the propanedial compounds were tested for their effectiveness in killing *Mycobacterium terrae*. *Mycobacterium terrae* is a type of mycobacterium and a type of bacteria. In paragraphs [0028] and [0031] it is disclosed that the *Mycobacterium terrae* was contacted with the germicidal solutions. Paragraph [0071] explains how they were contacted as follows: “In this test method, 9 mL of the

germicide to be tested is placed in a tube, put into a water bath and allowed to come to the desired temperature. One mL of the test organism, including at least 7 logs/mL of Mycobacterium terrae bacteria, is added to the 9 mL of the germicide to be tested.” Accordingly, the solution including the *Mycobacterium terrae* bacteria was added to the germicidal solution. **Accordingly, Applicants respectfully submit that this in-use germicidal solution absolutely is an example of a single isolated germicidal composition that includes *Mycobacterium terrae* bacteria.** Accordingly, claims 28, 29, and 30 are clearly fully supported by the original disclosure and comply with all requirements of 35 U.S.C. § 112, first paragraph.

Regarding claim 27, in paragraph [0091] it is disclosed that the germicidal compositions may be used to kill **other** than *Mycobacterium terrae* bacteria. In paragraph [0020] it is disclosed that:

[0020] *A potential problem with known germicides that are already being used in commerce is that microorganisms may become resistant to the germicides. Microorganisms, such as tuberculosis (emphasis added), which were once relatively easy to kill, may become more resistant to the germicides, and correspondingly more difficult to kill. Certain bacteria are already becoming resistant to glutaraldehyde. New germicides with even small structural differences from known or currently employed germicides may counteract or compromise the microorganisms resistance or tolerance. As such, the new germicides disclosed herein may greatly advance the arts of disinfection and sterilization (emphasis added).*

Accordingly, paragraph [0020] clearly discloses that the new germicides disclosed in the patent application may greatly advance the arts of disinfection and sterilization by killing microorganisms such as tuberculosis. Furthermore, it is well known in the art that germicidal solutions of the type disclosed may be used to contact tuberculosis when used for disinfection or sterilization, since tuberculosis may be found in hospitals. Accordingly, claim 27 is clearly fully supported by the original disclosure and complies with all requirements of 35 U.S.C. § 112, first paragraph.

Claim 37 is fully supported by original claim 8. Furthermore, claim 37 is fully supported in Example 4, Example 11, and in a combination of Example 4 and Example 11. Accordingly, claim

37 is clearly fully supported by the original disclosure and complies with all requirements of 35 U.S.C. § 112, first paragraph.

Accordingly, Applicants respectfully submit that the rejection of claims 27-30 and 37 is inappropriate and should be withdrawn.

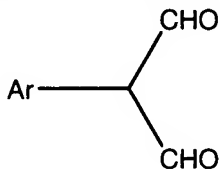
35 U.S.C. §103(a) Rejection - Klimko

The Examiner has rejected claims 1, 3-4, 7-8, 10, 19-20, 22-23, 25, 31, 34 and 37 under 35 U.S.C. §103(a) as being obvious over *Zhurnal Obshchei Khimii*, 1959, 29, Pg. 4027-4029 by Klimko et al. (hereinafter "Klimko") in view of U.S. Patent No. 6,429,220 issued to Yagi et al. (hereinafter "Yagi"), U.S. Patent Application No. 2004/0071653 A1 by Bratescu et al. (hereinafter "Bratescu") and *Tetrahedron*, 55, 1999, pg. 2389-2400 by Duran-Patron et al. (hereinafter "Duran-Patron"). The Applicants respectfully submit that the present claims are allowable over Klimko, Yagi, Bratescu, and Duran-Patron.

Claim 1 pertains to a germicidal composition comprising:

"a diluent;

an amount of a compound of the following formula effective to kill mycobacterium:



wherein Ar is an aryl group selected from the group consisting of phenyl, 4-pyrimidinyl, and 2-(2-nitro-3-formyl-phenyl); and

a corrosion inhibitor".

Klimko reportedly discloses the synthesis of phenylmalonaldehyde. However, Klimko does not teach or suggest that phenyl-propanedial is germicidal. Furthermore, Klimko does not teach or suggest what amount of phenyl-propanedial is effective to kill mycobacterium. Still further, Klimko does not teach or suggest that a corrosion inhibitor be included in composition with phenyl-

propanedial, or the desirability of including a corrosion inhibitor in a composition with phenylpropanedial. These points do not appear to be in dispute.

As understood by Applicants, the Examiner appears to be asserting that it would be obvious to combine the phenylmalonaldehyde disclosed in Klimko with the germicidal compositions disclosed in Yagi, Bratescu, and Duran-Patron on the grounds that dialdehyde functionalities are allegedly known to possess potent antibiotic properties as allegedly taught by Duran-Patron. See e.g., the middle of page 5 of the present Office Action. Applicants respectfully disagree.

To clarify, Duran-Patron more precisely discloses that most (not all) saturated and unsaturated dialdehydes possess “*potent bioactivities*” (emphasis added). See e.g., the first sentence of the Introduction. Furthermore, a bioactive dialdehyde is not necessarily **antibiotic**. The term “bioactive” even encompasses the possibility that the dialdehyde promotes the growth of bacteria, rather of killing the bacteria.

Furthermore, Applicants respectfully submit that Duran-Patron does not teach or reasonably suggest that dialdehyde functionalities in general are germicidally effective enough to kill **mycobacterium**. As discussed in the reference “*Sterilization or Disinfection of Medical Devices*”, which is included herewith as Attachment 1 (two pages), killing mycobacterium is a task that is practically met by high-level disinfectants and intermediate-level disinfectants, but not by low-level disinfectants:

“There are three levels of disinfection: high, intermediate, and low. High-level disinfection kills all organisms, except high levels of bacterial spores, and is effected with a chemical germicide cleared for marketing as a sterilant by the Food and Drug Administration. Intermediate-level disinfection kills mycobacteria, most viruses, and bacteria with a chemical germicide registered as a “tuberculocide” by the Environmental Protection Agency (EPA) (emphasis added). Low-level disinfection kills some viruses and bacteria with a chemical germicide registered as a hospital disinfectant by the EPA”.

Killing mycobacterium is a difficult task for a germicide. There are relatively few known dialdehydes that meet the criteria of intermediate-level disinfectants or better. Simply put, there are

literally hundreds of dialdehydes, but very few of these dialdehydes are practically useful for killing mycobacterium.

Duran-Patron discusses the fungal antibiotic properties of a few structurally related botrydial dialdehydes. However, it is well established that even though compounds may have similar functional groups, for example two aldehyde groups, the compounds may nevertheless have drastically different properties. As stated in Duran-Patron, “*small structural changes may modulate the biological activities considerably*” (see e.g., Introduction at page 2389). Even among the structurally similar botrydial related compounds investigated in Duran-Patron, the activities were found to be quite “*diverse*” and the differences to be “*dramatic*”. See e.g., the bottom of page 2393. Even small structural changes had dramatic reductions in antibiotic properties and made some of the compounds “inactive”.

Applicants respectfully submit that such dramatic changes in antibiotic activities for relatively small structural changes in structurally closely related compounds is indicative of a substantial degree of unpredictability. The degree of unpredictability would be even greater, if more significant structural changes were made. Significantly, the structural dissimilarity between the compounds of claim 1 and the compounds investigated by Duran-Patron are very considerable.

Submitted herewith as Attachment 2 (three pages) is a declaration pursuant to 37 C.F.R. § 1.132, signed by Dr. Jean-Yves Maillard, an expert in the field of antimicrobial activity. In this declaration, Dr. Maillard states his opinion that it is completely unreasonable for the Examiner to assume that any given dialdehyde would be germicidally effective enough to kill mycobacterium. Dr. Maillard expressed his opinion that the interactions between aldehydes and cells are too complex to allow for simple prediction based on chemical structure alone. Furthermore, Dr. Maillard expressed his opinion that the activities against *Bacillus subtilis* reported in Duran-Patron cannot be extrapolated to mycobactericidal activity and that the use of acetone in experiments in Duran-Patron may have changed cell permeability.

Accordingly, Applicants respectfully submit that it is simply unreasonable and inappropriate to assume, based on Duran-Patron, that there is any reasonable expectation of success that any given dialdehyde selected from the large number of possible dialdehydes, regardless of its structure, would be germicidally effective enough to kill mycobacterium. Accordingly, there is no teaching or reasonable suggestion to combine the phenylmalonaldehyde synthesized in Klimko with the germicidal composition disclosed in Yagi, Bratescu, or Duran-Patron.

For at least one or more of these reasons, claim 1 and its dependent claims are believed to be allowable. Independent claim 19 and its dependent claims are believed to be allowable for similar reasons.

The Examiner has rejected claims 27-30 and 33 under 35 U.S.C. §103(a) as being obvious over Klimko in view of Yagi, Bratescu, Duran-Patron, and J. Appl. Bact. 30(1), 78-87 by Rubbo et al. (hereinafter "Rubbo").

Applicants respectfully submit that Klimko should not be combined with Rubbo, since there is no teaching or reasonable suggestion that the phenylmalonaldehyde discussed in Klimko is germicidal, let alone germicidally effective enough to kill mycobacterium. The discussion above is pertinent to this point. Accordingly, Applicants elect at this time not to address other aspects of the rejection of these dependent claims.

Conclusion

In view of the foregoing, it is believed that all claims now pending patentably define the subject invention over the cited art of record and are in condition for allowance. Applicants respectfully request that the rejections be withdrawn and the claims be allowed at the earliest possible date.

Request For Telephone Interview

The Examiner is invited to call Brent E. Vecchia at (303) 740-1980 if there remains any issue with allowance of the case.

Request For An Extension Of Time

The Applicants respectfully petition for an extension of time to respond to the outstanding Office Action pursuant to 37 C.F.R. § 1.136(a) should one be necessary. Please charge our Deposit Account No. 02-2666 to cover the necessary fee under 37 C.F.R. § 1.17 for such an extension.

Charge Our Deposit Account

Please charge any shortage to our Deposit Account No. 02-2666.

Respectfully submitted,

BLAKELY, SOKOLOFF, TAYLOR & ZAFMAN LLP

Dated: 4/30/07

By Brent E. Vecchia
Brent E. Vecchia, Reg. No. 48,011
Tel.: (303) 740-1980 (Mountain Time)

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Attachment 1



Department of Health and Human Services
Centers for Disease Control and Prevention

Sterilization or Disinfection of Medical Devices

The following principles are applicable to most questions CDC receives about sterilization or disinfection of patient-care equipment. However, these statements are not comprehensive.

General Principles

1. In general, reusable medical devices or patient-care equipment that enters normally sterile tissue or the vascular system or through which blood flows should be sterilized before each use. Sterilization means the use of a physical or chemical procedure to destroy all microbial life, including highly resistant bacterial endospores. The major sterilizing agents used in hospitals are a) moist heat by steam autoclaving, b) ethylene oxide gas, and c) dry heat. However, there are a variety of chemical germicides (sterilants) that have been used for purposes of reprocessing reusable heat-sensitive medical devices and appear to be effective when used appropriately, i.e., according to manufacturer's instructions. These chemicals are rarely used for sterilization, but appear to be effective for high-level disinfection of medical devices that come into contact with mucous membranes during use (e.g., flexible fiberoptic endoscopes).
2. Disinfection means the use of a chemical procedure that eliminates virtually all recognized pathogenic microorganisms but not necessarily all microbial forms (e.g., bacterial endospores) on inanimate objects. There are three levels of disinfection: high, intermediate, and low. High-level disinfection kills all organisms, except high levels of bacterial spores, and is effected with a chemical germicide cleared for marketing as a sterilant by the Food and Drug Administration. Intermediate-level disinfection kills mycobacteria, most viruses, and bacteria with a chemical germicide registered as a "tuberculocide" by the Environmental Protection Agency (EPA). Low-level disinfection kills some viruses and bacteria with a chemical germicide registered as a hospital disinfectant by the EPA.
3. Heat stable reusable medical devices that enter the blood stream or enter normally sterile tissue should **always** be reprocessed using heat-based methods of sterilization (e.g., steam autoclave or dry heat oven).
4. Laparoscopic or arthroscopic telescopes (optic portions of the endoscopic set) should be subjected to a sterilization procedure before each use; if this is not feasible, they should receive high-level disinfection. Heat stable accessories to the endoscopic set (e.g., trocars, operative instruments) should be sterilized by heat-based methods (e.g., steam autoclave or dry heat oven).
5. Reusable devices or items that touch mucous membranes should, at a minimum, receive high-level disinfection between patients. These devices include reusable flexible endoscopes, endotracheal tubes, anesthesia breathing circuits, and respiratory therapy equipment.
6. Medical devices that require sterilization or disinfection must be thoroughly cleaned to reduce organic material or bioburden before being exposed to the germicide, and the germicide and the device manufacturer's instructions should be closely followed.
7. Except on rare and special instances (as mentioned below), items that do not ordinarily touch the patient or touch only intact skin are not involved in disease transmission, and generally do not necessitate disinfection between uses on different patients. These items

include crutches, bedboards, blood pressure cuffs, and a variety of other medical accessories. Consequently, depending on the particular piece of equipment or item, washing with a detergent or using a low-level disinfectant may be sufficient when decontamination is needed. If noncritical items are grossly soiled with blood or other body fluids, follow instructions outlined in the section on **HIV-related sterilization and disinfection** of this information system.

Exceptional circumstances that require noncritical items to be either dedicated to one patient or patient cohort, or subjected to low-level disinfection between patient uses are those involving:

1. Patients infected or colonized with vancomycin-resistant enterococci or other drug-resistant microorganisms judged by the infection control program, based on current state, regional, or national recommendations, to be of special or clinical or epidemiologic significance
or
2. Patients infected with highly virulent microorganisms, e.g., viruses causing hemorrhagic fever (such as Ebola or Lassa).

If you have questions about a low- or intermediate-level disinfectant and certain sterilants, contact the manufacturer, or the Antimicrobial Program Branch, Environmental Protection Agency (EPA) hotline (703) 308-0127 or email: info_antimicrobial@epa.gov. The EPA is the federal regulatory agency for low- or intermediate-level disinfectants and some sterilants.

If you have questions about high-level disinfectants (sterilants), or how to clean, disinfect or sterilize a particular medical device, first contact the manufacturer of the product. If you are unable to obtain sufficient information in this manner, contact the Food and Drug Administration (FDA) regional office or the FDA Center for Devices and Radiological Health at (301) 443-4690. FDA is the federal regulatory agency for safe and effective use of medical devices and is now also responsible for regulation of chemical sterilants.

Date last modified: August 20, 2002

Content source: Division of Healthcare Quality Promotion (DHQP)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION
 SAFER • HEALTHIER • PEOPLE

Attachment 2



O Our Docket No: 56301.P5007

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Zhu et al.

Examiner: Yong S. Chong

Application No: 10/769,598

Art Unit: 1617

Filed: January 30, 2004

For: Germicidal Compositions Containing)
 Phenylmalonaldehyde-Type Compounds)
 or Mixtures of Phenylmalonaldehyde-Type)
 Compounds and Phthalaldehydes, and)
 Methods of Using such Compositions)
for Disinfection or Sterilization)

Commissioner of Patents and Trademarks
 Washington, D.C. 20231

DECLARATION PURSUANT TO 37 C.F.R. §1.132

Sir:

I, Dr. Jean-Yves Maillard, presently hold the position of Senior Lecturer in Pharmaceutical Microbiology, at the Welsh School of Pharmacy, at Cardiff University, Wales, United Kingdom. I have extensive research experience in the antimicrobial activity of microbiocides, the mechanisms of action of antimicrobial agents, and the interaction between micro-organisms and microbiocides. I have numerous publications on these subjects. Currently, I am the Chief Editor of "Letters in Applied Microbiology" and a member of the Editorial Board for the Journal of Antimicrobial Chemotherapy. I am the recipient of the WH Pierce Memorial prize 2003. I am also the recipient of the BPC Conference Science award 2003. Overall, I am considered to be an expert in the field of antimicrobial activity and mechanisms of action of, and microbial resistance to, microbiocides and antimicrobial agents.

I have reviewed the Office Action mailed 12/28/2006 and in particular have closely reviewed pages 4-8 of this Office Action. I have carefully considered the Examiner's remarks on these pages 4-8 concerning the 35 U.S.C. §103(a) rejection of certain claims on Klimko et al. translated from Zhurnal Obshchei Khimii, 1959, Vol. 29, No. 2, pg. 4027-4029 (hereinafter "Klimko"), U.S. Patent No. 6,429,220 to Yagi et al. (hereinafter "Yagi"), U.S. Patent Application 2004/0071653 A1 by Bratescu et al. (hereinafter "Bratescu"), and Durán-Patrón et al., Tetrahedron 55 (1999) pp. 2389-2400, (hereinafter "Durán-Patrón"). I have also carefully considered the Examiner's remarks concerning the 35 U.S.C. §103(a) rejection of certain claims on Klimko, Yagi, Bratescu, Durán-Patrón, and Rubbo, (1967), J. Appl. Bact. 30 (1), 78-87.

I have reviewed Klimko sufficiently to understand the Examiner's application of this reference and have carefully read the abstract. I have reviewed Yagi sufficiently to

understand the Examiner's application of this reference and have carefully read column 6, lines 52-67. I have reviewed Bratescu sufficiently to understand the Examiner's application of this reference and have carefully read paragraphs [0183], [0184], and [0196]. I have carefully read through and carefully considered all of pages 2389-2400 of Durán-Patrón. I have reviewed Rubbo sufficiently to understand the Examiner's application of this reference.

It is my understanding that the Examiner has taken the position that it would be obvious to assume that any dialdehydes, including the compounds referred to in present claims 1, 7, 11, 14, and 19, would have a reasonable expectation of success of being germicidally effective enough to kill mycobacterium based on what is disclosed in Durán-Patrón. It is my understanding that the Examiner believes that the disclosure of Durán-Patrón suggests that dialdehyde functionalities in general possess sufficiently potent antibiotic properties to lead one to believe that any dialdehyde would have a reasonable expectation of success of being germicidally effective enough to kill mycobacterium.

I respectfully disagree with the Examiner's position and interpretation of Durán-Patrón. In my opinion, Durán-Patrón does not disclose that any given dialdehyde would have a reasonable expectation of success of being germicidally effective enough to kill mycobacterium. Accordingly, in my opinion, there is no reason to conclude based on Durán-Patrón that the compounds referred to in present claims 1, 7, 11, 14, and 19 would have a reasonable expectation of success of being germicidally effective enough to kill mycobacterium. The compounds discussed in Durán-Patrón are structurally significantly different than those of present claims 1, 7, 11, 14, and 19 and even Durán-Patrón indicates that small structural changes may modulate the biological activities considerably. Rubbo also reported that biocidal activity correlated to chemical structure, further refuting the notion that any given dialdehyde would have sufficient efficacy to kill mycobacterium.

The Examiner has asserted that "compounds and properties are inseparable". However, when one refers to activity against micro-organisms, in particular, mycobacterium, such a statement has no practical meaning, since antimicrobial activity can not always be predicted based on chemical structure alone. The interactions between aldehydes (usually considered as highly reactive alkylating agents) and the target cells are too complex to allow for simple prediction based on chemical structure alone. Indeed, aldehyde-based compounds will have multiple target sites against micro-organisms. The number of target sites affected, the level of interactions with these target sites, and the subsequent alterations or destruction of these target sites will produce no-effect, a mild-effect (e.g. growth inhibition) or a lethal effect. Such effect can not be predicted by understanding the chemical structure of the molecule alone.

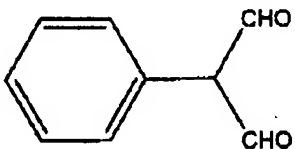
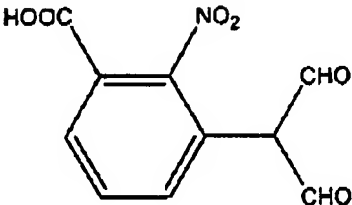
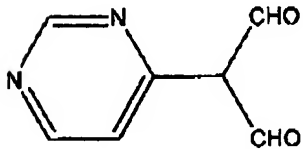
The Examiner's comments are based heavily on the Durán-Patrón paper. From a practical point of view, I noted that the experiments described in this paper did not allow for repeatability in results. In addition the use of acetone might have added changes in cell permeability, enhancing the interaction-cell active (i.e. phenomenon commonly known as potentiation) and hence the results observed might not have reflected solely on the action with the aldehydes. In addition, this paper described activity against *Bacillus subtilis* and the results can not be extrapolated to mycobactericidal activity. Finally Durán-Patrón describes simple measurement of activity as minimum inhibitory

concentration, but does not inform on the mechanism of action or interaction with microbial macromolecules. The discussion in this paper is thus speculative assuming interactions based on an understanding of chemical structures, but such speculation are not corroborated with solid experimental proof; i.e. the binding to, and alterations of, specific target sites have not been investigated in this paper.

In my experience and opinion, it is completely unreasonable for the Examiner to assume that any given dialdehyde would be germicidally effective enough to kill mycobacterium. What I have read of the Examiner's remarks and what is disclosed in Durán-Patrón does not change my opinion on this matter. In my experience, killing mycobacterium is well known to be a difficult task. I agree with the Applicants previously argued position that there are literally hundreds of dialdehydes, but very few would be practically useful for killing mycobacterium.

For clarity, I have reviewed the structures of the compounds of present claims 1, 7, 11, 14, and 19, which are reproduced below in Table 4 from the patent application.

Table 4

Compound	Name
	phenyl-propanedial
	3-(1-formyl-2-oxoethyl)-2-nitro-benzoic acid
	4-pyrimidinyl-propanedial

For clarity, based on my experience, and in my opinion, I cannot tell from the structures of these three compounds alone that they would be killing mycobacterium.

Respectfully submitted,

Date 26 APRIL, 2007


Dr. Jean-Yves Maillard